Therapeutic options in BK virus-associated interstitial nephritis

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CASE PRESENTATION

A female in her 30s developed renal failure secondary to mixed connective tissue disease-associated immune complex glomerulonephritis. Her past medical and family history was otherwise unremarkable. She underwent a pre-emptive renal transplantation from her mother, receiving induction with dacluzimab and had an uneventful post-transplant course. Her immunosuppressive regimen at discharge included prednisone 5 mg daily, mycophenolate mofetil 1000 mg twice daily, tacrolimus 4 mg twice daily, and prophylaxis with oral gancyclovir and trimethoprim–sulfamethoxazole, atenolol for hypertension, and famotidine, iron and calcium/vitamin D supplements. Her baseline serum creatinine after the transplant was 1.5 mg/dl.

Two years after receiving the transplant, she developed fever and dysuria and was treated for a presumed urinary tract infection (negative urine cultures). Her serum creatinine during this episode increased to 1.9 mg/dl and remained elevated in this range. Her physical examination was unremarkable and her blood pressure was 130/80 mm Hg. A renal ultrasound did not show any abnormalities. A renal biopsy was performed.

RENAL BIOPSY FINDINGS

Sampling for light microscopy consisted of a single core of renal cortex containing eight glomeruli, all of which appeared histologically unremarkable. There was diffuse, moderate to severe interstitial inflammation involving the entire cortex sampled, and composed of lymphocytes and less prominent plasma cells. The interstitial inflammation extended across tubular basement membranes to produce extensive tubulitis with multiple tubules containing greater than 10 lymphocytes. Proximal tubules also displayed diffuse degenerative changes and interspersed, enlarged, hyperchromatic nuclei with intranuclear viral inclusions typical of BK virus. This diagnosis was subsequently confirmed by immunohistochemical staining for SV40. There was moderate tubular atrophy and interstitial fibrosis involving 50% of the cortex sampled. Blood vessels appear unremarkable (Figure 1).

The renal biopsy findings were diagnostic of BK virus-associated interstitial nephritis (BKVIN). In the light of the diffuse distribution of the interstitial inflammation and tubulitis but more localized viral inclusions, the possibility of coexistent acute cellular rejection could not be excluded.

DISCUSSION

BK virus is a circular, double-stranded DNA virus.[1] In total, 70–85% of people are infected at some point in their lifetime, most frequently during childhood. The virus is likely transmitted through the respiratory route before establishing life-long latency in the urinary epithelium. It normally remains quiescent unless the immune system is impaired. It appears that T-cell mediated immunity keeps viral replication in check; renal transplant patients with antibodies directed against BK virus may still progress to nephropathy. Studies show that viral reactivation occurs in patients after solid organ transplantation, bone marrow transplantation, and in patients with human immunodeficiency virus/acquired immunodeficiency syndrome. Despite case reports of BKVIN after heart transplantation and in patients with HIV/AIDS, BKVIN as a cause of renal dysfunction is rare outside of renal transplantation.[2,3]

Reactivation of BK virus may manifest in several different forms (Table 1). Asymptomatic viral replication, hemorrhagic cystitis, ureteral stricture, and viral interstitial nephritis/BK virus associated nephropathy have all been

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described. Among renal transplant recipients, the incidence of asymptomatic urinary shedding of virus ranges from 30 to 40%. The rate of BKVIN is lower, ranging from 1 to 10% in recent series, but may be increasing.[4] Rates of graft loss range from 10 to 80%. Most cases present within the first year after transplantation, although the disease can develop at any time. Risk factors for BKVIN have not fully been defined, but intensity of immunosuppression likely plays a key role. Treatment of rejection with intravenous steroids or antilymphocyte preparations increases the risk of developing BKVIN, but induction therapy with these preparations may not be associated.[5] It is suggested that the combination of tacrolimus (TAC) and mycophenolate (MMF) may be particularly potent at inducing BKVIN, but this too is not entirely clear. In a recent prospective study that included BK virus monitoring, 46% of patients on TAC + MMF developed viruria, as did 41% of patients on a regimen of cyclosporine and azathioprine (AZA). There was no independent effect of TAC, cyclosporine, MMF, or AZA on viruria or viremia.[6] Early reports suggest that immunosuppression superimposed on mechanical and ischemic damage could predispose to BK virus-associated ureteral stenosis.[7] Additional factors that may predispose to BKVIN include: male gender, white race, human leukocyte antigen mismatch, and ureteral stent usage.[4] The frequent presence of tubulitis makes concomitant rejection difficult to diagnose and may not respond to antirejection therapies.[8]

The recommendations of the 2003 consensus conference are that all renal transplant recipients should be screened for BK virus replication in the urine: (1) every 3 months during the first 2 years post-transplant; (2) when allograft dysfunction is noted; and (3) when allograft biopsy is performed. A positive screening result should be confirmed within 4 weeks and assessed by quantitative assays (e.g. BK viral load in plasma or urine). Definitive diagnosis of BKVIN requires allograft biopsy. If BKVIN and concurrent acute rejection is diagnosed, antirejection treatment should be considered, followed by reduction in immunosuppression.[4]

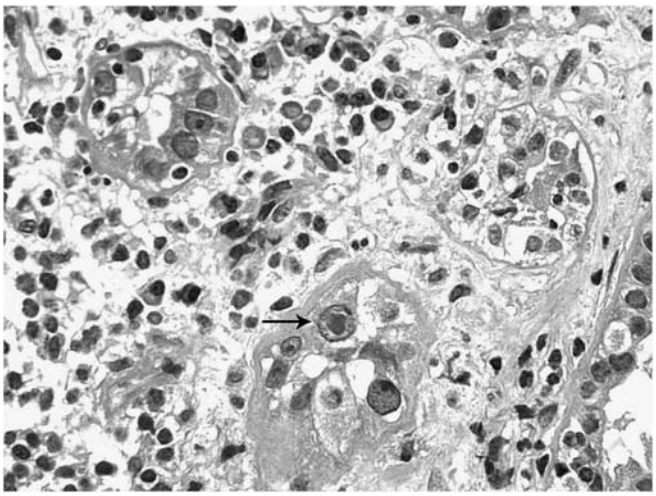

Figure 1 | BK virus inclusion in renal epithelial cells: nuclear enlargement with 'smudgy' appearance (arrow).

Table 1 | Spectrum of manifestations of BK virus infection

Asymptomatic viral shedding
Viral interstitial nephritis
Ureteral stricture
Hematuria, hemorrhagic cystitis

Treatment options for BKVIN

Treatment recommendations must be tempered by the fact that there are no well-conducted randomized trials on treatment strategies and no universally effective antiviral medications. Principles of treatment fall in two categories: modification of immunosuppression to restore antiviral immunity and specific antiviral therapy to reduce viral replication (Table 2).

Modification of immunosuppressive regimen

Prior to the discovery of medications with antiviral activity, treatment was limited to reducing immunosuppression. The optimal way to do this while providing adequate immunosuppression to prevent rejection remains debated. In a report on 100 patients by Ramos *et al.*,[9] patients maintained on a single immunosuppressant (TAC, cyclosporine, sirolimus) and prednisone were more likely to clear the virus and had less graft loss than those maintained on reduced dose of two immunosuppressants with continued prednisone. However, this was not a randomized trial. A successful immunosuppression reduction strategy may be gleaned from the prospective trial mentioned above.[6] Two hundred patients received rabbit antithymocyte globulin (Thymoglobulin® from Sangstat, Fremont, CA, USA) for induction followed by TAC or cyclosporine, prednisone, and AZA (low risk) or MMF (high risk) as the third drug. Patients were prospectively screened for BK virus replication with plasma and urine polymerase chain reaction, and patients with BK viremia had AZA or MMF withdrawn. If this was unsuccessful at clearing viremia, calcineurin inhibitor doses were reduced. Thirty-five percent of patients developed viruria; 11.5% developed viremia. Viremia resolved in 22 of 23 patients with reduction in immunosuppression, but only five of 23 cleared their viruria. Seven patients responded to withdrawal of AZA/MMF alone, two patients responded to reduction in calcineurin inhibitor dosage alone, six patients required cessation of AZA/MMF and additional reduction in calcineurin inhibitor, and seven patients cleared their infection

Table 2 | Treatment options for BK virus-associated nephropathy

Reduction of immunosuppression
Calcineurin-free immunosuppression
Cidofovir
Leflunomide

with standard tapering of immunosuppression after transplantation. Remarkably, there were no cases of biopsy-proven BKVIN in this cohort. Patients were only biopsied for graft dysfunction, not viremia, so mild cases of intrarenal viral replication may have been missed. Reduction in immunosuppression was associated with only one episode of rejection.

As an alternative to removing immunosuppressant agents, some authors have tried switching to calcineurin inhibitor-free regimens on the premise that renal epithelial cell toxicity of calcineurin inhibitors may be permissive to viral replication. Wali *et al.*[10] reported switching three patients from a regimen of TAC/MMF/prednisone to sirolimus/prednisone for biopsy-proven BKVIN. All three patients cleared their viremia at 18 months follow-up with improvement in mean serum creatinine from 1.8 to 1.5. It is important to recognize that this regimen does not distinguish a generalized effect of immunosuppression reduction from a specific benefit of sirolimus in BKVIN. Several cases of BKVIN have recently been reported in patients receiving sirolimus-based regimens.[11]

A final immunomodulation strategy that may become available in the future is the *ex vivo* manipulation of T cells to enhance BK virus-specific immunity.[12] This leaves open the possibility of providing specific immunity against the virus, while avoiding the increased risk of rejection associated with decreased immunosuppression.

Specific antiviral therapy

Cidofovir (Vistide®) is a cytidine nucleotide analog that has been used to treat cytomegalovirus (CMV) retinitis and JC virus associated progressive multifocal leukoencephalopathy. The use of cidofovir in renal transplantation is limited by its nephrotoxicity. In trials using cidovir to treat CMV retinitis, 50% of patients developed proteinuria (>100 mg/dl), and 24% developed serum creatinine concentrations >1.5 mg/dl. The first reported use of cidofovir specifically for BK virus infection was the successful treatment of hemorrhagic cystitis in a bone marrow transplant recipient.[13] Bjorang *et al.*[14] treated one renal transplant recipient with BKVIN with cidovir at a reduced dose to limit nephrotoxicity (taking advantage of the fact that cidovir is concentrated in the kidney providing adequate tissue concentration at a lower dose). Treatment was initiated at 0.25 mg/kg after 2 h of hydration with normal saline and was increased to 0.45 mg/kg per dose given every 2 weeks. Treatment resulted in clearance of virus from the blood and reduction in viruria. Since then, there have been several other case reports using cidofovir at doses ranging from 0.25 to 1 mg/kg every 2–3 weeks showing clearance of viremia in many.[15] These patients also underwent reduction in immunosuppression so it is difficult to distinguish the direct antiviral effect of cidofovir from the benefit of enhanced immune response. Unfortunately, many patients in these reports were also left with a significant amount of renal dysfunction and interstitial fibrosis.

Leflunomide (Arava®) is metabolized to its active metabolite A77 1726, which inhibits dihydroorate dehydrogenase, an enzyme involved in pyrimidine synthesis. Leflunomide has mainly been used to treat rheumatoid arthritis, but it has also been used in solid organ transplantation as primary immunosuppression. *In vitro* experiments suggest that leflunomide may also inhibit tyrosine kinase activity and that this inhibition of protein phosphorylation may be responsible for its antiviral effects.[16] Williams *et al.*[17] recently reported on outcomes of 17 patients treated with leflunomide for BKVIN. Fifteen of 17 patients showed either clearance of viremia (7 of 15) or reduction in serum viral load. Interestingly, the two patients without virologic response also showed persistent levels of A77 1726 below 40 μg/ml suggesting the need for a minimum therapeutic concentration. Serum creatinine stabilized or improved in the 15 patients with blood levels above 40 μg/ml. Leflunomide's main side effects are leucopenia, rash, and hair loss. The half-life of the active metabolite, A77 1726 is approximately 2 weeks. FK778, an analog of the active metabolite of leflunomide with a shorter half-life, is currently undergoing clinical trials both for maintenance immunosuppression in renal transplantation and in a trial to specifically treat patients with BKVIN.

Retransplantation in BKVIN

In patients who lose their allografts due to BKVIN, questions remain whether retransplantation is safe and whether transplant nephrectomy would reduce the rate of recurrent infection. Transplant nephrectomy has been associated with resolution of viremia, although immunosuppression was reduced at the same time.[18] Retransplantation in 10 patients after graft loss from BK virus infection was associated with recurrent infection in only one patient after a mean of 13.3 months follow-up. The recurrent infection occurred in a patient who had previously undergone transplant nephrectomy.[19] There are inadequate data to give firm recommendations on retransplantation after allograft loss due to BKVIN, but it seems prudent to ensure clearance of viremia, either through withdrawal of immunosuppression alone or possibly removal of the allograft if viremia persists.

FOLLOW-UP

In our patient, plasma BK virus titers at time of biopsy were 8×10^6 copies/ml and urine titers were $>1.3 \times 10^9$ copies/ml. The doses of TAC and sirolimus were reduced to target levels <5 ng/ml. Cidofovir 0.25 mg/kg/dose was administered at 2-weekly intervals. Her creatinine increased to 2.5 mg/dl. Repeat renal allograft biopsy again revealed diffuse and severe interstitial inflammation and tubulitis. Intranuclear viral inclusions were less prominently seen and a smaller percentage of cells stained positively for SV40 (a marker of BK virus infection). As a result, the patient was thought to possibly have BKVIN and concurrent acute cellular rejection. She received three-500 mg doses of intravenous methylprednisolone, and sirolimus was replaced with leflunomide at a

dose of 20 mg every other day. The patient was noted to be pregnant 5 months after starting leflunomide (contraceptive failure). Leflunomide was discontinued and 11 days of cholestyramine was administered to facilitate leflunomide removal. AZA was initiated at 75 mg/day at this time. She delivered a preterm infant after which leflunomide was resumed. Both mother and child are doing well at this time and the patient's serum creatinine at last follow-up (2 years after diagnosis of BK virus nephropathy) was 1.6 mg/dl. Her plasma BK virus (quantitative) remains negative.

CONCLUSION

Reactivation of BK virus is being increasingly recognized as a cause of allograft dysfunction and can lead to allograft loss. All renal transplant recipients should be screened for BK virus replication early in the transplant course or when allograft dysfunction is noted. Definitive diagnosis of BKVIN requires allograft biopsy. If BKVIN and concurrent acute rejection is diagnosed, antirejection treatment should be considered, coupled with subsequently reducing immunosuppression. Reduction of immunosuppression has been associated with clearance of viremia in asymptomatic patients. Leflunomide may be associated with clearance of viremia and stabilization of renal function. Cidofovir at low doses (0.25–0.33 mg/kg intravenously biweekly) without probenicid could be considered for refractory cases. Retransplantation after renal allograft loss to BKVIN remains a treatment option for patients who have cleared viremia.

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